Preclinical Evaluation of Cellular and Gene Therapy Products

Mercedes A. Serabian, M.S., DABT
FDA/CBER/OCTGT

Workshop on Counter Terrorism Products Regulated by CBER: Effective Strategies to Assist in Product Development

October 23, 2003
Bethesda, MD

serabian@cber.fda.gov

Requirements for Therapeutic Agent Approval

- Product development/characterization
  - Manufacturing & QC issues
- Toxicology/pharmacology development
  - *in vitro* and/or *in vivo* “proof-of-concept”
  - Acute & long-term testing designed to determine safety for clinical use
- Clinical development
  - Demonstration of safety & effectiveness in controlled clinical trials

Requirements for Therapeutic Agent Approval: Per the Animal Rule*

- Product development/characterization
  - Manufacturing & QC issues
- Toxicology/pharmacology development
  - *in vivo* "proof-of-concept"
  - Acute/long-term testing designed to determine safety for clinical use

*New Drug & Biological Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies are not Ethical or Feasible; FR 67: 37988-37998, 5/31/02

The Bottom Line...

Prior to the availability of human data, preclinical studies provide the sole source of data upon which activity [efficacy] & safety assessments are made

Goals of Preclinical Safety Evaluation

- Preclinical considerations for Phase 1/2 trials
  - To discern the mechanism of action [activity/toxicity] of the agent
  - Recommendation of initial **safe** dose & dose escalation scheme in humans
  - Identification of potential target organ(s) of toxicity/activity
  - Identification of parameters to monitor clinically
  - Identification of patient eligibility criteria
  - Terminate potentially unsuccessful development programs

Achievement of Goals for **All** Products – CBER/OCTGT/PTB

- "Pre-pre-IND" discussions..which lead to ..
- Pre-IND meetings
  - Establish safety of the product & intended pharmacological action
    - Preclinical **safety** issues
    - Preclinical "proof-of-concept"
    - Rationale for starting human dose
- Submission of IND

Pre-pre-IND Process

- Non-binding, informal scientific discussions between FDA and sponsor
  - Via telecons
  - Via CBER attendance at scientific meetings/workshops
  - Via outreach presentations (i.e., this workshop)
- Often minimal pre-read materials submitted by sponsor
- Targeted discussion of specific issue of interest
- Allows for information exchange – a “two-way street”

Pre-IND Process

- Non-binding, but formal meeting between FDA and sponsor
- Pre-read materials must be submitted by sponsor at least 30 days prior to meeting
- Formal minutes generated by FDA - sent to sponsor within 30 days after meeting
- Meeting emphasis - summary data and sound scientific principles to support use of a specific product in a specific subject population

The IND Review Process - Team Concept

- Regulatory project manager (RPM)
- Product reviewer (CMC)
- Preclinical reviewer (P/T)
- Clinical reviewer
- Biostatistics reviewer (when applicable)
- Consult Reviewer (when applicable)

How Are Animal Studies Integrated into the Proposed Clinical Plan?

- 21 CFR, part 312.23(a)(8)

Pharmacologic & Toxicologic Studies

  - "…adequate information about the pharmacological & toxicological studies…on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations."

OCTGT-Regulated Products: Application of 21 CFR 312.23

Repair, Replace, Restore, Regenerate

- Somatic cell therapy
- Gene therapy
- Xenotransplantation/therapy
- Device + biologic*
- Stem cell selectors*
- Tumor vaccines

(* in conjunction with CDRH)

Definition of Gene Therapy:

Introduction into the human body of genes or cells containing genes foreign to the body for the purposes of prevention, treatment, diagnosis or curing disease

Definition of Somatic Cell Therapy:

Administration to humans of:

- Autologous, allogeneic, xenogeneic cells
- Manipulated/processed to change their biological characteristics
  - Metabolic
  - Pharmacologic
  - Immunologic
- Not genetically modified

Preclinical Evaluation

- “Traditional” biologics vs. cellular & gene therapy agents
  - Similar general requirements for safety
    - Pharmacologic profiles
    - “Proof-of-concept”
    - Dose-response relationship
    - Toxicology profile

Preclinical Evaluation – Cellular & Gene Therapy Agents

- BUT… the approach by which safety data are obtained will differ

Gene Therapy	……..	**Cell Therapy**
	Animal models	
Biodistribution of vector		Migratory potential
Kinetics of gene expression		Cellular differentiation
		Cell phenotype expressed
		Anatomic/functional integration into host physiology
		Post-transplant survival
	Long-term toxicity	
	Reproductive toxicity	
Carcinogenicity/mutagenicity		Tumorigenicity (proliferative potential)

And…It's Not that Simple…

- Cellular Therapies
  - Infused*
  - Surgically implanted
    - Solid support (CBER + CDRH)
    - Encapsulated material (CBER + CDRH)
    - Aggregated form
- Gene Therapies*
- Cellular Therapy + Gene Therapy*

* May/may not require the use of an experimental delivery device

Regulatory Expectations for Toxicology Studies

21 CFR 312.23 – IND Content and Format

- Preclinical data should be adequate to support the proposed clinical trial
  - Range of doses, schedule and/or duration of treatment, route of administration should mimic those planned for the clinic
  - Sufficient safety data should be available to determine endpoints for monitoring in the clinic

The First Step… Pharmacology Studies

- What is the ability of a test article to induce the desired pharmacologic/biologic effect?
- Data may come from *in vitro* or *in vivo* studies, or both
  - Randomization/blinding/controls
- Demonstration of pharmacologic activity is the first step in the development of ANY new drug or biologic
- Collect safety data in the animal model of disease

Goals of Preclinical Pharmacology Studies

- Establish basis for conducting clinical trial
  - Feasibility/establishment of rationale
  - Kinetics of gene expression [for genetically modified products]
  - Pharmacodynamic effect - extent of functional correction
- Establish dose-response relationship - MED/OBD
- Optimize ROA/dosing regimen
- Rationale for species/model selection for further tests

Selection of Animal Species/Model

- Use of relevant species/model
  - Traditional
    - Normal animals; rodent & non-rodent
  - Non-traditional
    - Spontaneous disease
    - “Non-spontaneous” disease (induced, challenge)
    - Genetically modified animals
    - “Humanized” animals
  - Understand the limitations of the species/model
    - Availability, size, gender/age, housing needs, cost, ACUC concerns, technical feasibility, historical data, statistical limitations

Selection of Animal Species/Model

- Identify relevant model
  - Relevance to the specific clinical condition
    - Affect of disease on product
      - Increased sensitivity – good or bad?
  - Relevance to the therapeutic agent
    - Affect of product on disease
      - Exacerbation of current condition
      - Induction of new disease
- Use the data to support clinical use – risk/benefit

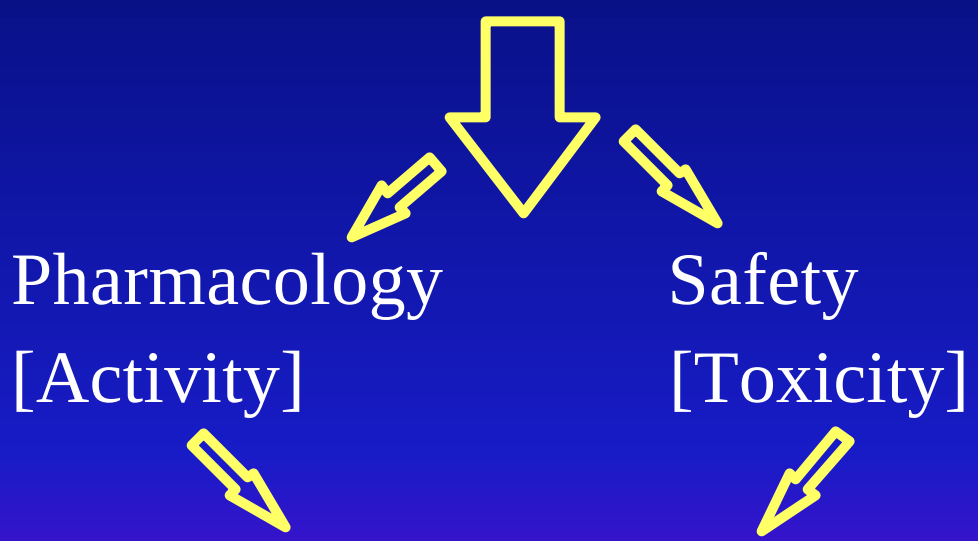
Use of Animal Models: Assessing Predictive Value

Animal*	Human**	Predictive?	
		Activity	Toxicity
Finding	Finding	☑	☑
No finding	No finding	☑	☑
No finding	Finding	**X**	**X**
Finding	No finding	**X**	**?**

* Multiple of human dose

** Human effective dose

Assessment of Safety/Activity - "Disease" Models



Sources of Preclinical Pharmacology Data

- Data in support of clinical trial can come from:
  - Well-controlled studies conducted in house
  - Published data in peer-reviewed journals
  - Cross-reference to similar products in previously submitted MF/INDs

Preclinical Safety Evaluation - Focus

- How can toxicological data derived from preclinical models provide information for the clinical management of potential toxicities?
  - Preclinical ID of specific toxicities = requirement for clinical monitoring
  - Predictiveness of the toxicology data for the human response
  - Impact on clinical development

The Next Step… Toxicology Studies – Gene Therapy

- Evaluate single/repeat exposure to the vector product (V)
  - Toxicities related to the delivery system
- Evaluate the safety of gene expression (T)
  - Persistence, level of expression *in vivo*
  - Identify target tissues/functional endpoints
  - Delayed toxicities/reversibility of toxicities
- Evaluate V + T
  - Characterize general toxicities
  - Identify specific toxicities
  - Characterize dose/exposure – NOAEL, MTD

The Next Step… Toxicology Studies – Cellular Therapy

- Evaluate the safety of the implanted cells (C)
  - Use cells intended for clinical use
    - May have to use non-human cells in analogous species
  - Influence of local microenvironment
    - Cell differentiation
    - Cell phenotype expression
  - Cell migration *in vivo*
  - Identify target tissues/functional endpoints
  - Delayed toxicities/reversibility of toxicities
  - Characterize general toxicities
  - Identify specific toxicities
  - Characterize dose/exposure – NOAEL, MTD

CBER Guidance – Endpoints Gene Therapy

- Emphasis on clinically relevant endpoints/ surrogate markers – e.g., angiogenic factor
  - Activity
    - Increased formation of collateral vessels
      - [Cardiac] Improved myocardial function (perfusion, flow, wall thickening)
      - [Peripheral] Increased vascular/capillary density to the ischemic limb
      - Presence of transgene in target tissues
  - Toxicity - local/systemic effects
    - Injection site rxn
    - Hypotension
    - Biodistribution/persistence of vector in nontarget tissues
    - Formation of Abs to vector/transgene
    - Acceleration of atherosclerosis
    - Inflammatory response in target/nontarget tissues

Preclinical Study Design – Vector Biodistribution

- Determination of distribution of the vector to intended therapeutic site/unintended site(s)
  - Presence of vector sequence via PCR analysis:
    - Dissemination of vector to the germline
    - Distribution of vector to non-target tissues
- Performance of biodistribution studies prior to Phase 1 when:
  - A new class of vector; no/little experience
  - A change in formulation
  - A change in the ROA w/ an established vector
  - Known potential of transgene to induce toxicity if aberrantly expressed in non-target tissues

CBER Guidance – Endpoints Cellular Therapy

- Emphasis on clinically relevant endpoints/ surrogate markers – e.g., cells (osteogenic/ dermal) + matrix
  - Activity
    - Contribution of each component
    - Graft performance -morphological/functional aspects
    - Effect of antimicrobial agents on graft performance
    - Time to/extent of engraftment
    - Prevention of morbidity
  - Toxicity - local/systemic effects
    - Contribution of each component
    - Implant site rxn
    - Ectopic bone formation
    - Formation of Abs to any foreign proteins
    - Inflammatory response in target/nontarget tissues
    - Biodegradation of matrix
    - Tumorigenicity

Regulatory Expectations for Toxicology Studies

21 CFR 312.23 (a)(8) – Pharmacology & toxicology

- For each toxicology study intended primarily to support safety, a full tabulation of data should be submitted
- Each study submitted should be performed per GLP, or an explanation provided

Sources of Toxicology Data

- Toxicity data in support of a clinical trial can come from:
  - GLP-compliant toxicology studies conducted by a contract laboratory
  - Well-controlled studies conducted in house
  - Published data in peer-reviewed journals
  - Cross-reference to similar products in previously submitted MF/INDs

The Bottom Line….

- Study design should answer specific questions regarding product safety/activity, using the relevant animal species/model
  - Determine a bioactive level (MED) & a safe level (NOAEL)
  - Determine margin of safety - toxic effect(s) vs. beneficial effect(s) for the product
  - Determine a safe starting clinical dose/dose escalation scheme

[Some] Limitations of Preclinical Studies

- Lack of information/understanding regarding fundamental biochemical and physiological mechanism of axn
- Target site/receptor absent in test species
- Treatment does not lead to sufficiently sustained protein concentrations at target site
- Lack of available animal model(s) of disease
- Extrapolation to relevant physiological state

Findings Resulting in Possible Modification to Clinical Trial(s)

- Serious life-threatening events
- Unexpected toxicities
- Delayed effects
- Irreversible effects
- Additional findings in long-term studies
- Enhanced toxicity in an animal model of disease
- Similar adverse findings displayed in several models
- Tumor development

CBER Approach to Preclinical Safety Evaluation – for **All** Products

- Data-driven
- Problem-solving, creative
- Should be based on best available science, technology to date
- Careful design of preclinical studies results in judicious use of animals

Take Home Messages

- The most useful approach to preclinical safety evaluation of cellular & gene therapies should:
  - Utilize rational, scientifically-designed, & problem-solving study designs
  - Be based on the best available technology/ methods
  - Follow FDA guidances, ICH, & the CFR
  - Include the judicious use of animals

Take Home Messages

- Sponsors are encouraged to utilize relevant animal species & animal models of disease in preclinical studies ….

  …keeping in mind that..

- No one species will be representative or predictive for all humans [including humans]

Take Home Messages

- A better understanding of fundamental & physiological mechanisms will help to provide a scientific basis for safer & faster clinical development
- The goal: To avoid inappropriate use of the product
- The goal: To optimize the predictive value of the product

Take Home Messages

- **Sponsors should contact CBER at an early stage of preclinical development to discuss study designs to answer the necessary questions**

- **Early and frequent interactions with CBER P/T reviewers are encouraged**

For Additional Information…

- Guidance for Industry: Providing Evidence of Effectiveness for Human Drug and Biological Products

  http://www.fda.gov/cber/guidelines.htm
- Guidance for Human Somatic Cell Therapy and Gene Therapy
  http://www.fda.gov/cber/gdlns/somgene.pdf
- ICH Documents
  http://www.fda.gov/cber/guidelines.htm

The CBER Connection…

Pharm/Tox Branch
OCTGT/DCEPT

(301) 827-5102 [phone]
(301) 827-0910 [fax]


LAB INITIO
by Nick D Kim
My friends, as a result of our experimentation, we have just lost a dear and valued colleague....
On the other hand, we have just gained a publication.
NICK